

# Radiotherapy in non-Hodgkin lymphomas

M. Gospodarowicz<sup>1</sup>

<sup>1</sup>Princess Margaret Hospital, Ontario Cancer Institute, Toronto, Ontario, Canada

Most patients with localized non-Hodgkin lymphoma (NHL) who receive radiotherapy (RT) are treated with the intent of achieving local control of disease [1]. A palliative approach is used only when, due to the condition of the patient and/or the extent or location of the disease, a radical course of treatment carries no chance of local control. Knowledge of histology, extent and pattern of disease is essential to select the appropriate therapeutic strategy. Involved field RT is routinely used, whether for cure or local control. The recognition of the high risk for occult distant disease mandates the use of chemotherapy in all cases of diffuse large cell lymphoma or similar histologies. For localized disease, the initial decision for patients treated with curative intent is the use of a combined modality approach—chemotherapy and RT, or a local treatment alone with RT. The choice is predicated upon the inherent risk of occult distant disease, availability of curative chemotherapy and the potential need for local control. Patients with stage III and IV are routinely treated with chemotherapy alone.

The aim of RT is to deliver an adequate dose of radiation to the target volume to ensure local control. The design for a proper course of RT must take into account the extent of disease, the appropriate margins, routes of lymphatic and possible extranodal spread, and the radiation tolerance of normal tissues and organs. Dose fractionation parameters must assure local control with acceptable acute and late toxicity. The technique should guarantee reproducibility of treatment on a daily basis. Custom-designed fields should be used to conform to the target volume while keeping the volume of irradiated normal tissues to a minimum. The use of CT simulation with delineation of target volumes including the gross tumour volume (GTV), the clinical target volume (CTV), which includes the microscopic disease extent, and planning target volume (PTV), which takes into account variation in the location of the GTV and CTV. Three dimensional conformal RT (3D CRT) or intensity modulated RT (IMRT) may be used to shape the dose distribution. It is important to note that when RT follows chemotherapy in CMT protocols, RT is usually started 4–6 weeks following the last course of chemotherapy to minimize the drug–radiation sensitization effect.

## follicular and MALT Lymphomas

The standard approach to RT in follicular lymphomas [2, 3] is involved field (IF) RT. With moderate doses of radiation (30–35 Gy in daily fractions in 4 weeks), the local control rate

is >95%. Because of occult systemic disease, relapse in unirradiated sites occurs in >50% of patients within the next 5–15 years. Treatment at the time of recurrence requires chemotherapy, although RT is also very useful in selected cases. In palliative approaches in patients with disseminated or recurrent follicular lymphomas, high response rates are observed even with a low dose of 4 Gy (2 × 2 Gy). Because of the indolent nature of follicular lymphomas, long-term follow-up is required to test the effects on survival of any new treatment approaches. The relative rarity of localized disease, the long follow-up required and competing mortality from unrelated causes, form significant barriers to the conduct of clinical trials in this disease.

MALT lymphomas, indolent B-cell tumors, present with stage I–II disease in 70–90% of cases. MALT lymphomas arise most commonly in the stomach, orbit, thyroid, salivary glands, breast, lung, skin and bladder. When applied, IF RT to 25–35 Gy results in a >95% local control rate with a significant proportion of patients being cured. Although MALT lymphomas are usually indolent, transformation into aggressive large cell lymphomas occurs. Current experience with MALT lymphomas shows cure with local therapy in a significant proportion of patients [4].

## large cell lymphomas (diffuse large B-cell lymphoma)

The treatment of localized large cell lymphomas [5, 6] has evolved from the use of RT alone to the routine use of combined modality therapy (CMT). The best results with RT alone were obtained in small trials that included meticulously staged patients with favorable prognostic factors. Pathologic stage I patients have 10-year relapse-free rates of ~90% with RT alone. Similarly stage IA or IIA patients with favorable clinical attributes treated with RT alone to a dose of 35 Gy achieved a 77% relapse-free rate at 10 years. In the early 1980s, several phase III trials showed the superiority of chemotherapy and radiation. CMT became the standard approach, with the administration of three to eight courses of doxorubicin-containing chemotherapy followed by IF RT. Brief chemotherapy with three courses of CHOP followed by radiation (30 Gy or equivalent) produces excellent results in patients with non-bulky (<10 cm) stage I–II with 10-year PFS of 74% and overall survival (OS) of 63% after a median follow up of 7.3 years. With the success of chemotherapy in advanced NHL, the role of routine RT in localized disease was questioned

The author reports no relationships with companies whose products or services are mentioned in this manuscript.

and trials of chemotherapy alone for localized non-bulky diffuse large cell lymphomas have been conducted. In the Eastern Cooperative Oncology Group (ECOG) trial, 345 patients with stage I and II disease (including bulky tumors) were treated with eight courses of CHOP chemotherapy and randomized to receive consolidation IF RT or no further treatment [7]. For those with complete response randomized to RT, the dose was 30 Gy, while all partial response patients received 40 Gy. With an intent-to-treat analysis, the 6-year disease-free survival was 53% in the CHOP arm and 69% in the CMT arm ( $P = 0.05$ ). Patients with a partial response to CHOP received RT and their 6-year failure-free survival was 63%, similar to those achieving a complete response to CHOP. This trial confirmed the benefit of IF RT who received CHOP chemotherapy in terms of disease control. However, no OS benefit was evident in this trial, but the trial had inadequate power to detect a clinically important (10%) survival difference.

In the SWOG trial of 401 patients with stage I–II non-bulky (<10 cm) disease CHOP  $\times$  8 was compared with CHOP  $\times$  3 followed by IF RT [8]. The radiation dose was 40 Gy with a boost to 50 Gy for partial responders. Patients treated with both CT and RT had a superior 5-year progression-free survival (PFS: 77% versus 64%,  $P = 0.03$ ) and OS rates (82% versus 72%,  $P = 0.02$ ). The adverse risk factors included stage II disease, age >60 years, increased lactate dehydrogenase (LDH) and ECOG performance status of >1. This raised a concern that patients with adverse prognostic factors might have had inadequate chemotherapy in the CMT arm. The decision to use fewer than six courses of chemotherapy should be based on known prognostic factors that predict for tumor burden. We currently recommend that patients without unfavorable risk factors (i.e. non-bulky disease, nodal stage I, normal LDH, no B symptoms and good performance status) be treated with three courses of CHOP followed by IF RT [9]. Patients with one or more risk factors should be approached with a longer course of chemotherapy (six cycles) and RT. These studies are now less relevant as the addition of rituximab has been shown to improve the outcomes in all CD20-positive lymphomas. Rituximab should be used in combination with CHOP for diffuse large B-cell lymphoma (DLBCL).

The general principles of RT in CMT protocols is to use IF RT to a dose of 30–35 Gy over 3–4 weeks. Not all studies demonstrate the benefit of RT. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) LNH 93-4 trial studied patients aged >60 years, with no adverse IPI factors, and CHOP  $\times$  4 + RT was not superior to CHOP  $\times$  4 alone. It might well be that four cycles of CHOP was inadequate therapy for this group of patients and the addition of RT could not compensate for the suboptimal chemotherapy. In the GELA LNH 93-1 trial, patients <60 years treated with an intensive chemotherapy regimen (ACVBP followed by sequential consolidation treatments) had more favourable event-free survival and OS than those treated with CHOP  $\times$  3 + RT. Whether the addition of RT is beneficial to CT alone when regimens are more intensive than CHOP (e.g. CHOP + rituximab, or the ACVBP regimen) awaits further testing in phase III trials.

## other histological subtypes

Less common, but distinct clinicopathologic entities including peripheral T-cell lymphoma anaplastic large cell lymphoma and mantle cell lymphoma may present with localized disease. At present, the treatment strategies for these entities are similar to those for large cell lymphomas, with the use of CMT. In a study of a small number of patients with stage I–II mantle cell lymphoma, the use of an RT-containing regimen was associated with an improved disease control and survival. As the knowledge regarding their clinical behavior, genetic origin and etiology evolves over the next decade, innovative therapy will become available for these specific diseases.

## assessment of response and follow-up

Cure requires the ability to eradicate disease, therefore the key is to attain complete remission with the initial treatment plan. In patients treated with RT alone, response is usually assessed 4–6 weeks following the completion of therapy. Since the RT dose fractionation schedule is determined before treatment and is usually based on information regarding dose–response relationship and tolerance of tissues within the treatment volume, the presence of residual disease at the end of the treatment course is not an indication for additional RT. The assessment of response includes examination of the organ of presentation, repeat imaging studies if indicated, and a general examination to rule out disease progression. In patients treated with chemotherapy or CMT, where chemotherapy is used first, the response is assessed following one or two courses of chemotherapy and every 1–2 months thereafter. Chemotherapy is usually continued for two courses beyond attainment of complete remission [6, 7]. Gallium and PET scanning are useful in determining completeness of response as discussed earlier. However, it must be emphasized that FDG-PET cannot detect residual microscopic disease reliably. Currently, there is no evidence that in cases where standard therapy includes RT, a negative PET following chemotherapy implies that RT can be safely omitted. Studies are ongoing to evaluate the value of PET in patient selection for adjuvant RT. Although most recurrences in patients with aggressive lymphoma occur within 2–3 years following the diagnosis, late relapse occurs. Accordingly, prolonged follow-up is indicated. Some tumor locations pose special problems in follow-up assessment. For example, primary bone lymphoma often has persisting radiological and MRI abnormalities following treatment, and bone scan will show changes that cannot distinguish active disease from bone healing and remodeling. Residual mediastinal abnormalities are common, particularly if a bulky mass was present before treatment. Resolution of gallium avidity is helpful in such cases. PET scanning is useful in distinguishing viable lymphoma from fibrosis.

## management of primary extranodal lymphomas

Primary extranodal lymphomas account for ~25–45% of all lymphomas. The commonest is skin lymphoma, with the majority of cases being of T-cell histology. For B-cell histology,

the commonest are gastric lymphoma, Waldeyer's ring lymphoma (tonsil lymphoma being most frequent) and brain. Others include intestinal, lung, orbital adnexa, bone, extradural, thyroid, testis and other less common sites such as paranasal sinuses, breast, bladder, etc. Many have unique clinical characteristics. Because of the propensity of extranodal lymphomas to be truly localized, they have special importance to the radiation oncologist.

## radiation therapy for palliation

In the context of recurrent lymphomas, patients are encountered where no curative therapy is available. Radiation is an extremely effective modality in providing symptom relief and local control. Palliative RT has been underutilized in lymphoma because of a variety of other systemic treatment options. The following are situations where palliative RT should be considered: (i) stage III and IV indolent histology lymphoma, with localized bulky disease; (ii) relapsed or primary refractory NHL, any stage, with predominant localized disease, not eligible for intensive therapy because of old age, poor tolerance to chemotherapy or chemotherapy resistance; (iii) relapse of lymphoma post-autologous/allogeneic bone marrow transplantation; (iv) localized HIV-related lymphoma in patients not suitable for chemotherapy. When palliative RT is considered, it is important to establish the goal of therapy. Distinction should be made between attempts to achieve prolonged local control of disease, i.e. radical RT given for local control in a non-curative situation or RT given purely for the relief of symptoms. This decision is usually based on the clinical condition of the patient, the location, size and distribution of disease and the life expectancy of the patient. Radical RT for local control is not infrequently required for selected patients with chemotherapy-refractory aggressive histology lymphomas where the disease is predominately localized. In these situations, if normal tissue tolerance allows, it is desirable to deliver full-dose RT with 30–40 Gy in 10–20 fractions over 2–4 weeks. For rapidly progressive disease, accelerated fractionation should be considered, to 35–40 Gy in 20–30 fractions over 2–3 weeks, depending on volume and normal tissue tolerance. Acceptable regimens include 20 Gy in 5 fractions over 1 week, 25–30 Gy in 10–12 fractions over 2 weeks or 12–16 Gy in 2 fractions over 1 week.

For indolent lymphomas, excellent palliative responses to very low doses of radiation, such as 4 Gy given in two fractions have been observed. This was explained by the predominant mode of tumor cell death largely mediated by apoptosis. Response rates of 90% have been obtained in selected patients with this approach.

## radiation therapy techniques and prescription definitions

Due to the wide distribution of lymphoid tissues in the body, the technical aspects for planning of RT for lymphomas are highly dependent on the location and extent of the target volume. Examples of commonly used techniques, and selected issues that require special attention are discussed below. In

most cases, established techniques for other cancers presenting in the same sites can be adapted for treatment of lymphomas. In general, proper planning involves the appropriate use of immobilization devices, simulation, computed tomography-assisted tumor localization and planning, localization of adjacent normal tissues, custom-designed beam modifying devices and computerized calculation of isodose distributions. The goal of these steps is to achieve dose uniformity in the target volume to within  $\pm 5\%$  of the prescribed dose as specified by ICRU #24 and ICRU #62, while minimizing the RT dose to normal tissues. Intensity modulated RT will gain increasing importance in order to reduce any morbidity due to the exposure of organs at risk located adjacent to the target volume, particularly in instances of a repeat course of RT for relapsed disease. The support of allied health care disciplines including dental, nutritional, physiotherapy, social and psychology services is essential to good patient care.

The common terms used to describe the extent of RT are IF, extended field (EF) and total lymphoid (or nodal) irradiation (TLI or TNI). The use of these terms varies considerably in the literature. Generally, IF defines RT to the clinically involved region, with or without the first echelon adjacent lymph node region uninvolved by disease. EF defines RT to include the adjacent first echelon and the second echelon adjacent lymph node regions. With the routine use of CMT in the management of localized aggressive lymphoma, there has not been a trial to address whether whole nodal region coverage is still required, or whether a more limited coverage of the initially involved tumor mass with a margin will suffice. Total lymphoid RT implies treatment to all the major lymphoid regions, with the mantle and the inverted Y fields, with or without Waldeyer's ring fields. Its use at present is uncommon in NHL.

The dose of RT required to achieve local control varies depending upon histological type and tumor bulk. Follicular lymphoma and MALT lymphoma are more responsive to RT, and a dose of 30 Gy delivered in 15–20 fractions over 3–4 weeks results in local control rates in excess of 95%. For small cutaneous or orbital lesions RT doses of 25 Gy are sufficient to achieve 90–95% local control. Large cell lymphomas are less sensitive and require doses in the range 35–45 Gy. For low bulk disease treated with full courses of chemotherapy, excellent local control rates are obtained with 30 Gy [10], whereas for bulky lymphomas treated with CMT, a minimum dose of 35 Gy is required. Some centers routinely administer doses of 40 Gy, or up to 45–50 Gy in the combined modality setting. There are no randomized trials designed to determine the optimal dose of RT, and the practice has developed based on institutional experience, although higher doses are difficult to justify with excellent local control reported in patients who are in CR after chemotherapy.

In CMT protocols where chemotherapy is given before RT, there may be no abnormality or minimal residual disease at the time of RT planning. Therefore, in the determination of the target volume following CT, a decision is required to cover either the initial extent of disease or the post-CT nodal area, which can be normal or consist of minimal residual abnormalities. In general, if the disease displaced normal tissues without infiltration into surrounding extranodal tissues and there was a good response to CT, the radiation fields need not

cover the entire initial extent of the tumor volume. An example is a bulky mediastinal mass that did not infiltrate lung tissue and has reduced in size following chemotherapy, where the RT plan need only cover the post-chemotherapy abnormality. If, however, the disease was infiltrative initially into adjacent normal tissue, regression of the tumor mass still leaves microscopic residual disease in the infiltrated tissue and consideration must be given to adequately cover the initial disease extent. An example would be bone lymphoma where the RT volume following a good response to chemotherapy should include the pre-chemotherapy extent of disease.

### unresolved issues in the RT management of malignant lymphomas

The efficacy of RT in achieving local disease control has been accepted for many years. With excellent local control rates, attention has been focused on the optimization of chemotherapy. Rituximab is an important component of systemic therapy in DLBCL. Therefore the questions of optimal RT target volume or the optimal dose-fractionation schemes have not been prospectively tested in randomized trials. This is most evident in the management of diffuse large cell lymphoma with CMT, where the RT dose varies from 30 to 50 Gy depending on the center rather than disease characteristics. Similarly the RT volume can vary from IF, with or without inclusion of adjacent first echelon nodes, to EF. Currently, there are no phase III trials that address radiation therapy related issues in the management of NHL. Some of the controversies in the RT management of the NHL are:

- (i) the management of follicular lymphomas;
- (ii) optimal RT dose-fractionation, and CTV in combined modality protocols;
- (iii) the role of RT in stage I–II DLBCL;
- (iv) optimal RT in the setting of high-dose chemotherapy and stem cell support.

### conclusion

NHL represents a heterogeneous group of diseases that may affect any part of the body. They are characterized by

a tendency to present or progress to generalized disease. Therefore optimal systemic therapy is paramount. However, lymphomas are also characterized by a high degree of radioresponsiveness and therefore RT is an important modality in controlling these malignancies. Recent progress in biology and histopathology as well as cytogenetic techniques have allowed us to study homogeneous patient populations and have given an opportunity to reassess the role of RT in their management. Late effects of treatment manifesting as normal tissue toxicity and especially second cancers are continuing concerns following curative therapy. Attention to late morbidity while we devise treatments to improve the cure rate remains an important goal.

### references

1. Gospodarowicz M, Tsang R, Hodgson D et al. Lymphomas. In Hoskin P (ed): Oxford Textbook of Radiation Oncology. Oxford: Oxford University Press 2005.
2. Tsang RW, Gospodarowicz MK. Low-grade non-Hodgkin lymphomas. *Semin Radiat Oncol* 2007; 17: 198–205.
3. Tsai HK, Li S, Ng AK et al. Role of radiation therapy in the treatment of stage I/II mucosa-associated lymphoid tissue lymphoma. *Ann Oncol* 2007; 18: 672–678.
4. Tsang RW, Gospodarowicz MK, Pintilie M et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol* 2003; 21: 4157–4164.
5. Ng AK, Mauch PM. Role of radiation therapy in localized aggressive lymphoma. *J Clin Oncol* 2007; 25: 757–759.
6. Tsang RW, Gospodarowicz MK. Management of localized (stage I and II) clinically aggressive lymphomas. *Ann Hematol* 2001; 80 (Suppl 3): B66–72.
7. Horning SJ, Weller E, Kim K et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. *J Clin Oncol* 2004; 22: 3032–3038.
8. Miller TP, Spier CM, Rimsza L. Diffuse aggressive histologies of non-hodgkin lymphoma: treatment and biology of limited disease. *Semin Hematol* 2006; 43: 207–212.
9. Shenkier TN, Voss N, Fairey R et al. Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: an 18-year experience from the British Columbia Cancer Agency. *J Clin Oncol* 2002; 20: 197–204.
10. Horning SJ, Weller E, Kim K et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. *J Clin Oncol* 2004; 22: 3032–3038.